REMARKS

Claims 48, 49, 50, 55 through 68 and 70 through 75 are under examination in the application. Claims have been renumbered as requested by the examiner to eliminate the existence of two claims numbered 70.

The specification was objected to for including trademarks that are not capitalized or accompanied by generic terminology. The applicants acknowledge the objection and will submit the requested information upon a finding of allowable subject matter in the application.

The examiner objected to claims 48, 49, 50, and 59 through 63 for asserted improper dependency. The examiner, however, failed to state why the dependency is improper.

Claim 63 is amended here as suggested by the examiner.

The previously pending claims included two claims numbered at 70. Herein, the previously pending second claim numbered 70, and previous claims 71 through 74 are renumbered as claims 71 through 75.

Claims 48, 49, 50, 55, 56, 59 through 68, 70, 71, 72, 73, 74, and 75 were rejected under 35 USC 112, first paragraph, for assertedly lacking written description in the specification. Amendment to claims 71 and 72 (renumbered herein as claims 72 and 73) to correct typographical errors renders the rejection of those claims moot.

The written description rejections

The examiner maintained rejection of claims 48, 49, 50, 55, 56, 59 through 68, 70, 71, 73, 74, and 75 under 35 USC §112, first paragraph, for assertedly lacking written description in the specification. The examiner responded to the applicants' prior argument alleging that the claimed methods require structural limitation relating to the protamine fragments utilized. Specifically, the examiner asserted at page 7 of the Office Action, "No structural limitations are provided in the claims as to what said fragments look like." At the same page, the examiner asserted, "The claimed protamine is modified to achieve reduced immunoresponsiveness or toxicity, however the claims do not establish what those modifications are," and "a skill artisan would not be able to envision the detailed chemical structure of the genus of protamine fragments encompassed by the claims." At page 8, the

examiner argued "there is no indicia as to where in the native structure modifications will occur such that the resultant effect is a fragment of protamine that has reduced immunoresponsiveness or toxicity and will inactivate heparin or LMW heparin." At the same page, the examiner stated, "It is noted that applicant argues that the structure is well established, however, the fragments are claimed and they are not adequately described." Also at page 8, the examiner argued, "For example, claim 55 recites 'at least a purified protamine fragment effective to inactivate heparin or low molecular weight heparin, wherein said purified protamine fragment is bioactive, has a molecular weight between 400 and 2500 Daltons as determined by gel filtration and has reduced immunoresponsiveness or toxicity compared to native protamine,' however no correlation is made between function and structure. The applicants disagree.

First, the applicants have argued that a protamine fragment can be defined by the molecular weight which is expressly recited in the broadest claim. Specifically, the applicants have made the argument below which the examiner has not effectively rebutted.

> Firstly, the applicants direct the examiner's attention to the recited molecular weight range of the protamine fragment utilized in the recited method. If it is accepted, as asserted by the examiner at page 6 of the office action, that protamine structure comprises 31 amino acid residues, and the average molecule weight of an amino acid is between 110 and 115 daltons (stated without evidence, but can be supported if the examiner requests such evidence), then full length protamine has a molecular weight of approximately 3410 daltons to approximately 3565. Thus, the worker of ordinary skill would readily appreciate that the claims are directed to methods which,. In the broadest recitation, utilize a protamine fragment that is approximately 12% to approximately 73% the size of the full length protein is full length protamine is approximately 3410 daltons, or approximately 11% to approximately 70% the size of full length protamine if full length protamine is approximately 3565 daltons. The applicants submit that this molecular weight range clearly distinguishes the protamine fragments recited in the claimed methods.

Certainly it must be understood that for any known amino acids sequence, all fragments can be predicted and are thus made available by the full length amino acid sequence. If the fragments are sorted by molecular weight, specific subsets are identified. With a 31 amino acid full length protein, all total fragments having a specific molecular weight range are therefore readily made available, and the amino acid sequence of each can be envisioned.

This point is expressly argued above and the examiner has put forth no arguments that suggests otherwise.

Moreover, inasmuch as the examiner has cited *Vas-Cath* for the proposition that the inventor must demonstrate possession of what is claimed, the applicants direct the examiner's attention to the results shown in Example 1. Therein, it is clear that the inventors were in fact in possession of the method as claimed. Low molecular weight protamine fragments were produced and utilized to inactivate heparin, and these biologically active fragments displayed lower immunoresponsiveness compared to full length protamine. The worker of ordinary skill in the art would therefore see that the inventors were in possession of what is claimed.

To the extent that the examiner believes that recitation of specific protease cleavage to produce protamine fragments would "give a skilled artisan a glimpse of what the structure [of the protamine fragment] would look like based on the enzyme used" [Office Action at page 8], then the examiner must conclude that the subject matter of claims 72 and 73 (as renumbered and amended herein) is allowable. This claim specifically recites numerous proteases used to generate the specific fragments and thus by the examiner's admission. Five a glimpse of what structure the recited protamine fragments would have.

Along this line, claims 74 and 75 (as renumbered herein) specifically recite structural amino acid residues in the protamine fragments which the specification teaches are needed for heparin inactivation. The recitation of these specific amino acid residues, in combination with the fact that full length protamine amino acid sequences were known in the art, provide yet another glimpse into the structure of the recited protamine fragments.

Accordingly, by the examiner's own reasoning, claims 72, 73, 74 and 75 must be found allowable even if the examiner maintains rejection of all other claims.

The applicants submit that a worker of ordinary skill in the art would appreciate by molecular weight only which fragments of protamine that are contemplated for use ion the methods of the invention, and that the specification demonstrates that the applicants were in fact in possession of what is being claimed. Thus, the applicants believe that all of the rejections for asserted lack of written description must be withdrawn.

CONCLUSION

In view of the amendments and remarks herein, the applicants submit that all claims are believed to be in condition for allowance and respectfully request notification of the same.

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Respectfully submitted,

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